

## Nitrous oxide in 2010: who will have the last laugh? (Part 3)

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### Introduction

In the first two parts of this series, the basic science of nitrous oxide (N<sub>2</sub>O) was reviewed and some of its claimed risks and benefits were analysed. In this, the third and final instalment, the remaining risks and benefits will be assessed and the alternatives to nitrous oxide will be evaluated. It will be shown that many of the claimed adverse effects of nitrous oxide either do not exist or are overstated. Nitrous oxide is a versatile agent with many potential benefits during all phases of anaesthesia.

### A critical appraisal of the risks and benefits of nitrous oxide (continued)

#### *Expansion of gas-filled spaces*

Nitrous oxide causes expansion of gas-filled spaces, or an increase in intracavitary pressure if the space is nonexpansile. This is a direct result of its physicochemical properties. Its low potency results in the use of high inspired concentrations, while the low blood/gas partition coefficient leads to a high propensity to partition into the gas phase. The fact that it is 40 times more soluble than N<sub>2</sub> means this diffusion into gas spaces occurs faster than nitrogen can diffuse out.

What are the clinical implications? I will briefly discuss and illustrate these with a number of clinical scenarios.

It has been reported that, at a concentration of 70%, nitrous oxide can double the size of a pneumothorax in 10 minutes, and triple it in 45 minutes.<sup>1</sup>

Nitrous oxide use in patients with intraocular gas bubbles may result in a three-fold increase in the volume of these bubbles after an hour's exposure, possibly leading to increased intraocular pressure and complications such as central retinal artery occlusion. A number of case reports have documented

adverse visual effects in patients with intraocular gas bubbles after nitrous oxide exposure during nonophthalmic surgery. The risk period is 7–10 days for sulphurhexafluoride (SF<sub>6</sub>), and 4–6 weeks for perfluoropropane, but may extend to 10 weeks for the latter agent. It is thus probably prudent to avoid nitrous oxide for 70 days after intraocular gas injection. In contrast, the use of nitrous oxide during ophthalmic surgery that involves injection of intraocular gas is probably insignificant.<sup>2</sup>

Nitrous oxide has also been shown to increase middle ear pressure and cases of tympanic membrane rupture have been reported.<sup>3</sup> It is thus best to avoid its use in middle ear procedures such as tympanic membrane grafting.

It is often stated that patients at risk of venous air embolism (VAE) should not be administered nitrous oxide. Some animal evidence points to a worsening of outcome after ongoing VAE with the use of a volatile/N<sub>2</sub>O anaesthetic. Interestingly, there was no such adverse effect with a barbiturate/N<sub>2</sub>O anaesthetic.<sup>4</sup> This study was, however, probably not representative of the real world clinical situation. I would argue that the rapidity of occurrence of a clinically significant VAE would mean that effective treatment, or patient demise, would have occurred before nitrous oxide diffusion has had time to have any significant effect. This is not an evidence-based opinion, but it does seem unreasonable to omit nitrous oxide solely because a patient is at risk of a VAE. The situation with patients undergoing cardiopulmonary bypass (CPB) is pathophysiologically different from that of a patient undergoing a craniotomy, for example, who has a sudden large VAE. It may thus be appropriate to avoid nitrous oxide in patients undergoing CPB.

Intestinal gas volumes have been reported to increase by 75–100% after two hours of exposure to nitrous

oxide, and 100–200% after four hours. In addition, delayed recovery of bowel function, delayed hospital discharge, and impaired intra-abdominal operating conditions have been claimed to result from nitrous oxide exposure.<sup>3</sup> A meta-analysis by Orhan-Sungur et al found that, although nitrous oxide resulted in a time-dependent increase in intraoperative bowel distension, this did not affect operating conditions, time to bowel movement, or hospital stay.<sup>5</sup> In a randomised trial of patients undergoing laparoscopic cholecystectomy, Taylor et al found identical intraoperative conditions regardless of whether or not nitrous oxide was used.<sup>6</sup>

In summary, nitrous oxide should be avoided in patients with gas-filled spaces where expansion or increased pressure could cause significant adverse effects, for example pneumothorax, pulmonary bullae, intraocular gas bubbles (when already in situ), tympanic surgery, or pneumocephalus. It is probably safe to use it in intraocular surgery, even if gas bubble injection is planned, and in patients undergoing surgery with a theoretical risk for VAE. In addition, despite previous concerns, nitrous oxide appears safe in intra-abdominal surgery.

Nitrous oxide diffuses into the cuffs of airway devices. Ong et al reported a consistent increase in endotracheal tube and laryngeal mask cuff pressure when nitrous oxide was used.<sup>7</sup> However, significant cuff hyperinflation occurred whether or not nitrous oxide was used. It thus appears that, whether nitrous oxide is used or not, cuff pressures should be monitored with a cuff manometer. The only disadvantage with nitrous oxide is the slight inconvenience of more frequent cuff pressure assessment. It is also worth noting that PVC cuffs are less susceptible to this effect.<sup>8</sup>

#### **Awareness**

It is claimed that nitrous oxide reduces awareness. This assertion has a reasonable pharmacokinetic and pharmacodynamic basis.<sup>9</sup>

From a pharmacokinetic perspective, the ability to accurately estimate the blood concentration of nitrous oxide from the end-tidal concentration offers a significant advantage over propofol total intravenous anaesthesia (TIVA), for example. This advantage of nitrous oxide may even extend to the volatiles. To illustrate this, with propofol target controlled infusion, the blood concentration of propofol may be 20% above or below the target concentration. The blood concentration of isoflurane, after 15 minutes of stable end-tidal concentrations, may be 35% below the end-tidal concentration. With nitrous oxide, however, after 15 minutes the blood concentration is only 10% less than the inspired concentration.<sup>9</sup>

Pharmacodynamically, the fact that nitrous oxide has an analgesic effect with a similar dose-response profile to its amnestic effect should make recall of a noxious surgical stimulus less likely. To this end, nitrous oxide has been shown to have a more potent amnestic effect for a noxious stimulus than the volatile anaesthetics.<sup>9</sup>

A number of studies indicate a reduced risk of awareness with the use of nitrous oxide.<sup>9, 10, 11</sup> Most startling is the meta-analysis by Tramer et al, which reported that the number needed to treat (NNT) to prevent a case of awareness with nitrous oxide was only 46. There are a number of criticisms of the awareness component of this study but, to put it into perspective, the NNT to prevent awareness with bispectral index (BIS) monitoring may be close to 1,250. So, even if Tramer is incorrect by a factor of 10, nitrous oxide would still be more effective than BIS in preventing awareness.

#### **Environmental**

Nitrous oxide acts as a greenhouse gas in the troposphere and, via photochemical conversion to nitrogen oxides, contributes to destruction of the ozone layer in the stratosphere.<sup>6, 9, 12</sup> It is the third most climatologically significant greenhouse gas, and has 300 times the global warming potential of CO<sub>2</sub> over 100 years.<sup>13</sup> Medical sources, however, only contribute 1% of nitrous oxide emissions.<sup>12</sup> Even if we, as “green anaesthetists”, were to completely cease using nitrous oxide, the environmental effect would be negligible.<sup>6</sup>

#### **Teratogenicity and foetotoxicity**

Prolonged exposure to nitrous oxide has been shown to be teratogenic and foetotoxic in animal studies.<sup>3, 14</sup> This included exposure of up to 24 hours on the first day of gestation, and is unlikely to be applicable to clinical practice. Clinical studies in human pregnancy are obviously limited, but do not show an increase in foetal loss or abnormalities with nitrous oxide exposure.<sup>3</sup> In fact, there appears to be no significant association between anaesthesia in general and foetotoxicity and teratogenicity.<sup>14</sup>

#### **Occupational exposure**

The possible adverse effects of occupational exposure to nitrous oxide have created much heated and often emotional debate. Sanders et al have compiled an excellent overview of this topic.<sup>14</sup> According to the authors, nitrous oxide is supposed to have reproductive effects (impaired fertility, increased abortion, and increased risk of low birth weight and small for gestational age babies), neurological effects (neuropathies and neurocognitive dysfunction) and haematological effects, and genotoxicity.

They make the key point that many of these claims have arisen from animal studies which have used high exposures that are inconsistent with workplace exposures, or from studies published prior to adequate workplace scavenging. With modern scavenging that adheres to occupational health guidelines, occupational exposure to anaesthetic gases is low. Occupational exposure limits (OEL) represent the maximum allowable 8-hour time-weighted average (TWA) exposure to N<sub>2</sub>O. These range from 25 TWA ppm in the USA and Australia, to 100 TWA ppm in South Africa and the UK. Prior to modern scavenging, exposures were routinely 1,000–2,000 ppm.

They also note that the studies are tainted by reporter bias, poor response rates, inadequate controls, and inconsistent results. In addition, there are a number of confounders, like shift-work, physical strain, age and exposure to toxins.

The conclusions that can be drawn from this review are reassuring. The available studies do not substantiate concerns about reproductive toxicity in a scavenged environment. There is no evidence that nitrous oxide alone cause genotoxicity, although some evidence suggests that exposure to mixed gases may increase markers of genotoxicity. The clinical effects of this are not known. There is no reliable evidence to suggest an increased risk of neuropathies with routine occupational exposure. Exposure to levels approximately a thousand times above occupational limits is required to impair neurocognitive performance. Haematological toxicity does not occur at occupational exposure limits.

This is comforting, but it remains our responsibility to safeguard our wellbeing by ensuring that sound occupational health guidelines are adhered to.

#### **Anaesthetic-sparing and cost-saving effects**

It is often claimed that nitrous oxide has a significant anaesthetic-sparing effect and that its use, consequently, results in a reduction in the cost of anaesthesia. As these two effects are so closely linked, they will be explored together.

As a general rule, the MAC of nitrous oxide and the volatiles are additive, with the MAC reducing effect of 60–70% nitrous oxide quantified at approximately 0.55–0.65.<sup>15</sup> This is substantiated by Jakobsson et al, who reported a 60% reduction in sevoflurane consumption with concomitant use of 66% nitrous oxide.<sup>16</sup> Muzi et al reported that 66% nitrous oxide reduced sevoflurane consumption during gas induction.<sup>17</sup>

Nitrous oxide also reduces propofol consumption. The administration of 66% nitrous oxide prior to propofol induction reduced the induction dose by 44%.<sup>6</sup> More importantly, nitrous oxide 65–67% has been found to reduce propofol infusion requirements by 25–50%.<sup>3, 6, 9</sup>

Nitrous oxide is, in addition, opioid sparing. This effect is well documented intraoperatively, but the influence on postoperative opioid consumption is not well established.<sup>1</sup> Nitrous oxide 70% has been found to be equivalent to 0.17 µg/kg/minute of remifentanyl, with 66% nitrous oxide equivalent to a whole blood remifentanyl concentration of 2 ng/ml.<sup>15, 18</sup>

It has also been reported that 70% nitrous oxide reduces the EC<sub>50</sub> of rocuronium by 20%.<sup>19</sup> This is probably of minimal impact economically but may theoretically alter the dosing of muscle relaxants.

What are the implications of the above? There is a reduction in the exposure to other anaesthetic agents, each with their own potential toxicities, and the risk of drug interactions is, theoretically, reduced. In addition, there are cost implications, which are of particular interest in this era of spiralling medical costs.

This is an extremely complex area, with little in the way of studies that take into account all the potential cost implications. In addition, it is very difficult to generalise cost results from one centre to another, especially if in different countries.

Muzi et al reported a 15% cost reduction in gas inductions in adults with the administration of sevoflurane/66% N<sub>2</sub>O instead of sevoflurane alone.<sup>17</sup> Jakobsson et al reported almost 60% reduction in the cost of sevoflurane anaesthesia with the use of 60% nitrous oxide.<sup>6, 16</sup> A study by Jakobson et al put a slightly different perspective on this. They reported that the cost of a sevoflurane/nitrous oxide anaesthetic, at a fresh gas flow of 3 l/min, was equivalent to the cost of sevoflurane, as a sole agent, at 1 l/min. Thus, for the same cost, one can benefit from the faster, easier titration afforded by a higher fresh gas flow.<sup>6</sup>

The reduction in propofol consumption with concurrent nitrous oxide administration is also likely to result in cost savings versus pure propofol TIVA. Hopkins reports that trials by Arellano et al and Visser et al demonstrated substantial cost savings, without additional costs from increased side effects, when anaesthetic techniques incorporating nitrous oxide were compared with propofol TIVA. It must be noted, though, that only the study by Arellano compared propofol TIVA with propofol/N<sub>2</sub>O, while Visser compared propofol TIVA with isoflurane/N<sub>2</sub>O.<sup>9</sup>

Nitrous oxide may also result in cost savings by reducing intraoperative opioid use. This is particularly so if it results in the reduction or elimination of remifentanil usage.

However, Baum reported that, if nitrous oxide is omitted from low-flow anaesthesia, the cost of increased volatile and opioid consumption may be offset by the saving arising from the complete removal of nitrous oxide from the insituition.<sup>12</sup> It is also claimed that eliminating nitrous oxide use makes closed circuit anaesthesia possible, which could result in significant savings. Whether closed circuit anaesthesia offers much financial advantage over minimal flow or low flow anaesthesia is debatable. The increased cost of soda lime and the practical difficulties of closed circuit anaesthesia also need to be taken into account.

On the balance of all the evidence, nitrous oxide definitely reduces the consumption of other anaesthetic agents, and probably results in a reduction in anaesthetic costs. It appears that only the complete elimination of nitrous oxide from a hospital could counterbalance the cost savings from reduced agent consumption. This is because it would eliminate the costs of not only nitrous oxide but also, theoretically, of maintaining the nitrous oxide infrastructure (e.g. nitrous oxide pipelines). A further factor to consider, however, is the cost of the disposables and infusion pumps necessary to run TIVA or remifentanil infusions. Ultimately, each hospital should perform its own detailed anaesthesia-related cost analysis to determine the financial implications of various anaesthetic agents. In the interim, I would suggest that nitrous oxide is most likely to result in significant cost reductions when used with the more expensive agents such as sevoflurane, desflurane, propofol, and remifentanil.

#### *Effects on induction*

Many practitioners claim that nitrous oxide offers advantages during gas induction in children. Its use prior to the addition of sevoflurane provides some sedation and better tolerance of the latter agent's odour. It is also believed to provide a smoother, quicker induction.

These benefits also extend to gas inductions in adult patients. Muzi et al reported a 27% reduction in the time to acceptable intubating conditions in adults undergoing gas inductions with sevoflurane/66% N<sub>2</sub>O versus sevoflurane alone.<sup>17</sup> They also reported a 50% reduction in breath holding and a 38% reduction in expiratory stridor in the nitrous oxide group. Hall et al similarly reported a 14% reduction in induction time, a smoother induction with fewer adverse events, and

a greater first time success rate for LMA insertion when 66% nitrous oxide was added to sevoflurane during a vital capacity induction technique in adults.<sup>6</sup> Ng et al showed a 41% reduction in induction time with the addition of nitrous oxide prior to propofol induction.<sup>6</sup> Nitrous oxide also reduces the pain from propofol injections, another useful characteristic during induction.

#### *Effects on emergence*

Nitrous oxide undergoes rapid elimination and thus, theoretically, results in faster recovery than when high concentrations of the primary agent are used alone. This is supported by a number of studies. Servin et al and Sukhani et al reported a 16–24% reduction in the time to orientation with N<sub>2</sub>O/propofol vs propofol TIVA. Jakobson et al found a 40% reduction in time to orientation with sevoflurane/N<sub>2</sub>O vs sevoflurane alone.<sup>6</sup> Einarsson et al showed that isoflurane/N<sub>2</sub>O resulted in an earlier return to spontaneous breathing, and earlier extubation, than MAC equivalent isoflurane alone.<sup>3</sup> Although the recovery time with desflurane is unlikely to be improved by concomitant use of nitrous oxide, the potential for significant cost containment still makes this an attractive combination. It should be noted that recovery from a nitrous oxide-based anaesthetic may appear delayed if BIS monitoring is used to titrate depth of anaesthesia. This is because BIS monitoring is insensitive to nitrous oxide and, if not taken into account while using BIS with nitrous oxide, it will result in a greater depth of anaesthesia than expected.<sup>6</sup> As noted before, Brodsky et al found that the risk of diffusion hypoxia is overrated and of minimal clinical significance. Therefore, it appears that nitrous oxide offers potential benefits during emergence without significant adverse effects.

#### *Miscellaneous*

There are a number of miscellaneous benefits associated with nitrous oxide.

Nitrous oxide is an extremely versatile agent. Aside from its use as an anaesthetic adjunct, nitrous oxide has been used extensively as a labour analgesic. It is also safe and effective when used for procedural sedation or analgesia in adults and in children.<sup>20, 21</sup> It may also be used as an effective alternative to EMLA for venous cannulation in children.<sup>22</sup>

The ease of use of nitrous oxide, the extensive clinical experience with this agent and the familiarity of anaesthetists with its use are further points in its favour. Despite the many criticisms of nitrous oxide, 165 years of use attest to its remarkable safety. It is noteworthy that it undergoes no metabolism, has no significant drug interactions, does not cause hepatotoxicity or

nephrotoxicity, has no adverse reactions with soda lime, and is not a trigger for malignant hyperthermia.

### Alternatives

If we were to abandon the use of nitrous oxide on the advice of the naysayers, what would the alternatives be? One would want an agent that has analgesic and amnestic effects, acts rapidly, and is of short duration. The closest current matches are xenon and remifentanyl.

Xenon, with a MAC of 70%, offers the advantage that it can be used as a sole anaesthetic agent. It demonstrates cardiovascular stability, is neuroprotective and has no direct adverse environmental effects. It is, however, extremely rare and exorbitantly costly.<sup>6</sup> In addition, its manufacture is energy intensive and thus it has indirect adverse environmental effects. Xenon is thus not a practical alternative to nitrous oxide.

Remifentanyl is the closest contender. As with all opioids, it is a potent analgesic but a poor amnestic agent.<sup>9</sup> It has been reported that 66–70% nitrous oxide is equivalent to 2 ng/ml or 0.17 µg/kg/minute of remifentanyl.<sup>16, 18</sup> A combination of remifentanyl and midazolam has been suggested as a more appropriate alternative to remifentanyl alone.<sup>9</sup> There are, however, a number of potential problems with remifentanyl. It is expensive. As with all intravenous agents, there

is greater pharmacokinetic variability compared to nitrous oxide. It is more complex to administer. It causes significant respiratory depression and is not suitable for use in spontaneously breathing patients. It causes cardiovascular depression, with a dose-dependent decrease in mean arterial pressure and cerebral perfusion pressure, and may cause significant bradycardia. It has also been associated with acute opioid tolerance and an increased risk of postoperative pain, hypertension and agitation.<sup>6, 9, 23</sup>

It is clear that nitrous oxide is a unique agent, with no readily available replacement.

### Conclusion

Nitrous oxide is a unique drug. It is a safe agent with many positive pharmacokinetic and pharmacodynamic attributes and it deserves an important place in anaesthetic practice in 2010 and beyond. Although modern anaesthesia would not collapse in the absence of nitrous oxide, or any other anaesthetic agent, it would be much poorer for the loss.

This review has shown that most of the commonly quoted adverse effects of nitrous oxide are grossly overstated, of little clinical impact, or are outweighed by its benefits. Table I shows the evidence-based risks and benefits, a very different picture from the conventional wisdom shown in Table I of Part 2 of the series.

**Table I:** Evidence-based risks and benefits of nitrous oxide in routine clinical practice

Benefits		Risks	
<b>Cardiovascular</b>	Haemodynamic stability	<b>Expansion of air-filled spaces</b>	Pneumothorax
<b>Respiratory</b>	Reduced respiratory depression		Pulmonary bullae
	Improved oxygenation		Pneumocephalus
<b>Awareness</b>	Reduced		Middle ear
<b>Anaesthetic sparing</b>	Volatiles	<b>PONV</b>	Intraocular +/-
	Opioids		Limited effect
<b>Cost-effective</b>		<b>Pulmonary hypertension</b>	Mild exacerbation
<b>Induction</b>	Faster		
	Smoother		
	Fewer adverse events		
<b>Emergence</b>	Rapid		
<b>Miscellaneous</b>	Versatile		
	Simple to use		
	Extensive experience		
	Familiarity		
	Established safety profile		

As with any agent, paying attention to its indications and contraindications is a prerequisite for its safe use. After examining the available evidence, the contraindications no longer comprise the traditional daunting list. In fact, even when taking a conservative view of the current evidence, the contraindications should only consist of the four categories noted below.

**Table II: Contraindications to nitrous oxide use<sup>14</sup>**

<b>Absolute</b>	Potential significant adverse effects from expansion of gas-filled spaces (as noted above)
	Known deficiency of enzyme or substrate in methionine synthase pathway
<b>Relative</b>	Pulmonary hypertension
	Severe, acute raised intracranial pressure?

This review has also shown that we need to look beyond the often formulaic approach to preoperative assessment, and the traditional approach to premedication. We need to look to a future where our perioperative management is specifically tailored to the individual's phenotype and genotype.

This is only one of the many exciting avenues of nitrous oxide-related research that still need to be explored. The risk-benefit ratio for the use of nitrous oxide in patients at high cardiac risk is another fascinating area of study and, with this in mind, the results of ENIGMA II are eagerly awaited. We are also in need of a current, local cost analysis and a large-scale study into its effects in traumatic brain injury

It is time to suspend the general bias against nitrous oxide and grant it the place it deserves in anaesthetic practice in 2010. We might even find that this faithful old anaesthetic dog has some exciting new tricks to show us.

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